A Division of The McGraw-Hill Companies

Note: Dr. Fauci and Dr. Longo's works as editors and authors were performed outside the scope of their employment as U.S. government employees. These works represent their personal and professional views and not necessarily those of the U.S. government.

Harrison's
PRINCIPLES OF INTERNAL MEDICINE
Fourteenth Edition

1234567890 DOWDOW 9987
ISBN 0-07-020291-5 (COMBO)
0-07-020292-3 (VOL 1)
0-07-020293-1 (VOL 2)
0-07-912013-X (SET)

FOREIGN LANGUAGE EDITIONS
Arabic (Thirteenth Edition)—McGraw-Hill Libri Italia srl (est. 1996)
Chinese (Twelfth Edition)—McGraw-Hill Book Company–Singapore © 1994
Croatian (Thirteenth Edition)—McGraw-Hill Libri Italia srl (est. 1996)
French (Thirteenth Edition)—McGraw-Hill Libri Italia srl © 1995
German (Thirteenth Edition)—McGraw-Hill Libri Italia srl © 1995
Greek (Twelfth Edition)—Parissianos © 1994
Italian (Thirteenth Edition)—McGraw-Hill Libri Italia srl © 1995
Japanese (Eleventh Edition)—Hirokawa © 1991
Portuguese (Thirteenth Edition)—McGraw-Hill/Nueva Editorial Interamericana © 1995
Spanish (Thirteenth Edition)—McGraw-Hill Interamericana de España © 1994
Turkish (Thirteenth Edition)—McGraw-Hill Libri Italia srl (est. 1996)

This book was set in Times Roman by Monotype Composition Company. The editors were J. Dereck Jeffers, Martin J. Wonsiewicz, and Mariapaz Ramos Englis; editorial assistants were Rose Derario and Daniel J. Green. The production director was Robert Laffler. The index was prepared by Irving Tullar. The text and cover designer was Marsha Cohen/Parallelogram Graphics.

R.R. Donnelley and Sons, Inc., was the printer and binder.

Library of Congress Cataloging-in-Publication Data

Harrison's principles of internal medicine.—14th. ed./editors,
Anthony S. Fauci . . . [et al.]
p. cm.
Includes bibliographical references and index.
ISBN 0-07-020291-5 (1 vol. ed.).—ISBN 0-07-912013-X (2 vol. ed. : set).—ISBN 0-07-020292-3 (2 vol. ed. : bk 1).—ISBN 0-07-020293-1 (2 vol. ed. : bk 2)
1. Internal medicine. I. Harrison, Tinsley Randolph.
II. Fauci, Anthony S.
[DNLM: 1. Internal Medicine. WB 115 H322 1998]
RC46.H333 1998
616—dc21
DNLM/DLC
for Library of Congress 97-14184

Exh B

half-life, prednisone is the drug of choice except in infants, in whom hydrocortisone is usually used. In adults with late-onset adrenal hyperplasia, the smallest single bedtime dose of a long- or intermediate-acting glucocorticoid that suppresses pituitary ACTH secretion should be administered. The amount of steroid required by children with congenital adrenal hyperplasia is approximately 1 to 1.5 times the normal cortisol production rate of 27 to 35 μmol (10 to 13 mg) of cortisol per square meter of body surface per day and is given in divided doses two or three times per day. The dosage schedule is governed by repetitive analysis of the urinary 17-ketosteroids, plasma DHEA sulfate, and/or precursors of cortisol biosynthesis. Skeletal growth and maturation also must be monitored closely, since overtreatment with glucocorticoid replacement therapy retards linear growth.

Table 332-8

Laboratory Evaluation of Hirsutism-Virilizing Syndromes

	Ovarian		Adrenal			
	PCO	Ovarian Tumor	CAH	Adrenal Neoplasm	Cushing's Syndrome	Idiopathic
Urinary 17-ketosteroids, plasma DHEA sulfate	N↑	N	N↑	↑↑↑	N↑	N
Plasma testosterone	N↑	↑↑	N↑	N↑	N↑	N
LH/FSH ratio	N↑	N	N	N	N	N
Precursors of cortisol biosynthesis:						
Basal	N	N	N↑	N↑	N	N
Following ACTH infusion	N	N	↑↑	N↑	N	N
Cortisol following overnight dexamethasone suppression test	N	N	N	↑	↑	N

NOTE: CAH, congenital adrenal hyperplasia; PCO, polycystic ovary syndrome; N, normal; ↑, elevated.

HYPOFUNCTION OF THE ADRENAL CORTEX

Cases of adrenal insufficiency can be divided into two general categories: (1) those associated with primary inability of the adrenal to elaborate sufficient quantities of hormone and (2) those associated with a secondary failure due to inadequate ACTH formation or release (Table 332-9).

PRIMARY ADRENOCORTICAL DEFICIENCY (ADDISON'S DISEASE) The original description of Addison's disease—"general languor and debility, feebleness of the heart's action, irritability of the stomach, and a peculiar change of the color of the skin"—summarizes the dominant clinical features. Advanced cases are usually easy to diagnose, but recognition of the early phases can be a real challenge.

Incidence Primary insufficiency is relatively rare, may occur at any age, and affects both sexes equally. Because of the common therapeutic use of steroids, secondary adrenal insufficiency is relatively common.

Etiology and Pathogenesis Addison's disease results from progressive destruction of the adrenals, which must involve more than 90 percent of the glands before adrenal insufficiency appears. The adrenal is a frequent site for chronic granulomatous diseases, predominantly tuberculosis but also histoplasmosis, coccidioidomycosis, and cryptococcosis. In early series, tuberculosis was responsible for 70 to 90 percent of cases, but the most frequent cause now is *idiopathic* atrophy, and an autoimmune mechanism is probably responsible. Rarely, other lesions are encountered, such as adrenoleukodystrophy, bilateral hemorrhage, tumor metastases, amyloidosis, adrenomyeloneuropathy, familial adrenal insufficiency, or sarcoidosis.

Half of patients have circulating adrenal antibodies. Specific adrenal antigens to which autoantibodies may be directed include $P450_{c21}$. While most antibodies cause adrenal destruction, some antibodies cause adrenal insufficiency by blocking the binding of ACTH to its receptors. Some patients also have antibodies to thyroid, parathyroid, and/or gonadal tissue (see also Chap. 340). There is also an increased incidence of chronic lymphocytic thyroiditis, premature ovarian failure, type I diabetes mellitus, and hypo- or hyperthyroidism. The presence of two or more of these autoimmune endocrine disorders in the same person defines the polyglandular autoimmune syndrome type II. Additional features include pernicious anemia, vitiligo, alopecia, nontropical sprue, and myasthenia gravis. Within families, multiple generations are affected by one or more of the above diseases. Type II polyglandular syndrome is the result of a mutant gene on chromosome 6 and is associated with the HLA alleles B8 and DR3.

The combination of parathyroid and adrenal insufficiency and chronic mucocutaneous moniliasis constitutes type I polyglandular autoimmune syndrome. Other autoimmune diseases in this disorder include pernicious anemia, chronic active hepatitis, alopecia, primary hypothyroidism, and premature gonadal failure. There is no HLA association; this syndrome is inherited as an autosomal recessive trait. The type I syndrome usually presents during childhood, whereas the type II syndrome is usually manifested in adulthood. The mechanisms by which genetic predisposition and/or autoimmunity interact in the pathogenesis of these disorders are unknown.

Clinical suspicion of adrenal insufficiency should be high in patients with AIDS (see Chap. 308). Cytomegalovirus regularly involves the adrenal glands [so-called cytomegalovirus (CMV) necrotizing adrenalitis], and involvement with *Mycobacterium avium-intracellulare*, *Cryptococcus*, and Kaposi's sarcoma has been reported. Adrenal insufficiency in AIDS patients may not be manifest, but tests of adrenal reserve frequently give abnormal results. When interpreting tests of adrenocortical function, it is important to remember that medications such as rifampin, phenytoin, ketoconazole, and opiates may cause or potentiate adrenal insufficiency.

Adrenoleukodystrophy causes severe demyelination and early death in children, and adrenomyeloneuropathy is associated with a mixed motor and sensory neuropathy with spastic paraplegia in adults; both disorders are associated with elevated circulating levels of very long chain fatty acids and cause adrenal insufficiency. Familial adrenal insufficiency is an autosomal recessive disorder that causes unresponsiveness to ACTH secondary to mutations in the ACTH receptor. Adrenal hemorrhage and infarction occur in patients on anticoagulants and in those with circulating anticoagulants and hypercoagulable states, such as the antiphospholipid syndrome.

Clinical Signs and Symptoms Adrenocortical insufficiency caused by gradual adrenal destruction is characterized by an insidious onset of fatigability, weakness, anorexia, nausea and vomiting, weight

Table 332-9

Classification of Adrenal Insufficiency

PRIMARY ADRENAL INSUFFICIENCY

- Anatomic destruction of gland (chronic or acute)
  - "Idiopathic" atrophy (autoimmune, adrenoleukodystrophy)
  - Surgical removal
  - Infection (tuberculous, fungal, viral—especially in AIDS patients)
  - Hemorrhage
  - Invasion: metastatic
- Metabolic failure in hormone production
  - Congenital adrenal hyperplasia
  - Enzyme inhibitors (metyrapone, ketoconazole, aminoglutethimide)
  - Cytotoxic agents (mitotane)
- ACTH-blocking antibodies
- Mutation in ACTH receptor gene

SECONDARY ADRENAL INSUFFICIENCY

- Hypopituitarism due to hypothalamic-pituitary disease
- Suppression of hypothalamic-pituitary axis
  - By exogenous steroid
  - By endogenous steroid from tumor